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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,305	07/19/2006	Inpyo Choi	58049-00034	9091

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
12/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@jhkiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/597,305	CHOI ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 10/27/2010, in which claims 29 and 38 were amended. Claims 29 and 38 are pending in the instant application.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II and ferritin H chain (BC 012314) gene with traverse in the reply filed on 1/19/2009.

Claims 29 and 38 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the reply filed 10/27/2010, claim 29 was amended to require the step of "treating premature NK cells with an effective amount of ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein in vitro." Claim 38 was amended to require the step of "treating the premature natural killer cells, with an effective amount of ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein in vitro."

The first version of claim 29 was directed to the step of treating premature natural killer cells with an effective amount of ferritin H chain (BC012314) gene. Furthermore, the recitation of GenBank Accession No. BC012314 in the originally filed claims, in the context of ferritin H chain gene as a differentiation agent, is interpreted as intent to incorporate the nucleotide sequence of BC012314. GenBank Accession No. BC012314 (GI: 15126787, publicly available August 2001) is a nucleotide sequence record that describes a cDNA clone of the Mus musculus, ferritin heavy chain gene. The originally filed disclosure is directed only to the administration of ferritin H chain gene to cells (e.g., page 1, lines 8-12; page 3, lines 18-22; page 4, lines 21-24; pages 7-9; paragraph bridging pages 11-12). SEQ ID NO: 49 is the sequence of GenBank Accession No. BC012314.

The specification provides support for the culture of hematopoietic stem cells (HSCs) for six days to differentiate the cells to pNK cells, followed by the culture of the cells with OP9 stromal cells and IL-15 protein (e.g., page 24, lines 11-24; page 25, lines 1-13). Culture of the pNK cells in the presence of OP9 stromal cells and IL-15 protein resulted in the differentiation of the pNK cells to mNK cells (e.g., paragraph bridging pages 25-26).

Support could not be found in the originally filed specification for the treatment of premature NK cells with a combination of ferritin H chain gene of SEQ ID NO: 49 (BC012314) and IL-15 protein.

The reply filed 10/27/2010 asserts that support for the amendments can be found in the Examples section of US Patent Application Publication No. 2007/0042344.

The Examples section of the originally filed specification for the present application does not disclose the administration of ferritin H chain gene and IL-15 protein, at the same time, to premature NK cells. The Examples disclose the administration of IL-15 protein without ferritin H chain gene. The originally filed specification discloses the use of one or more genes to regulate the differentiation of natural killer cells (e.g., paragraph bridging pages 6-8). The originally filed specification discloses the use of one or more genes to regulate the differentiation of premature natural killer cells into mature natural killer cells, including the administration of the ferritin H chain gene (BC012315) (e.g., paragraph bridging pages 8-9). The originally filed specification does not disclose the administration of ferritin H chain gene and IL-15 protein to premature NK cells.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the passages that Applicant has provided do not provide support.

Claims 29 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 6/3/2010 but has been rewritten to address the amendments to the claims in the reply filed 10/27/2010.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 29 is drawn to a method of differentiating a hematopoietic stem cell (HSC) into a mature natural killer (mNK) cell, comprising (i) incubating the HSC in an incubator to produce premature NK cells; and (ii) treating the premature NK cells with an effective amount of ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein in vitro. Claim 38 is drawn to a method of differentiating a premature natural killer (pNK) cell to a mNK cell, comprising treating the pNK cells with an affective amount of ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein in vitro. The nature of the invention is complex in that the combination of ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein must be sufficient to differentiate HSCs or pNK cells to mNK cells.

Breadth of the claims: The claims are narrowly drawn to the administration of the ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein to premature NK cells to induce differentiation into mature NK cells.

Guidance of the specification: The specification asserts that ferritin H gene (BC012314)

is a differentiation regulating agent for natural killer cells (e.g., page 6). The specification asserts that the gene can be used to regulate the differentiation of pNK cells to mNK cells and to treat cancers (e.g., page 10, line 21 to page 12, line 23). The specification provides general guidance with regard to the administration of pharmaceutical formulations and envisions the use of oral or parenteral administration of the gene (e.g., page 12, line 25 to page 14, line 8).

The specification teaches the isolation of hematopoietic stem cells (HSCs) from the tibia and femur of a C57BL/6 mouse (e.g., paragraph bridging pages 22-23). The cells had over 96% purity (e.g., page 23, lines 9-13). The specification teaches that the mouse HSCs can be differentiated in vitro to pNK cells and further differentiated in vitro to mNK cells (e.g., page 23, line 15 to page 24, line 24). To differentiate the HSCs to pNK cells, the HSCs were cultured in RPMI complete medium supplemented with mouse SCF, mouse Flt3L, mouse IL-7, indomethacin, gentamycin and 10% fetal bovine serum (e.g., paragraph bridging pages 23-24). After 6 days in culture, the cells had differentiated to form pNK cells, which are CD122+ cells. The cells had over 92% purity (e.g., paragraph bridging pages 23-24). To induce the differentiation of pNK cells to mNK cells, the CD122+ cells were incubated with OP9 stromal cells in the presence of mouse IL-15 protein. On day 12, NK1.1+ cells were obtained (e.g., page 24, lines 11-24). Incubation of the pNK cells with IL-15 in the absence of OP9 stromal cells failed to induce the cells to differentiate to mNK cells based on the expression analysis of Ly49C/I and Ly49G2 (e.g., paragraph bridging pages 25-26).

The specification teaches the analysis of gene expression from HSCs, pNK and mNK cells using Serial Analysis of Gene Expression (SAGE) (e.g., page 26, line 9 to page 39, line 1). The specification discloses 30 different genes that were identified by the SAGE procedure as

specifically expressed at the pNK cell stage. These genes are recited in Table 4 at pages 35-37 of the specification. Ferritin H chain (BC012314) is included in this table at row 2. Further, the expression of Ferritin H chain was studied by RT-PCR using the primers disclosed as SEQ ID NOs: 27 and 28 (e.g., page 39, line 1 to page 41, line 18). By RT-PCR analysis ferritin H chain (BC012314) expression was detected in HSC, pNK, mNK (-OP9) and mNK (+OP9) (Figure 4B). The specification teaches that IL-15 nucleic acid was only detected n HSC and pNK cells (e.g., page 32), unlike ferritin H chain (BC012314).

Existence of working examples: The working examples demonstrate that more than incubation of HSCs is required to obtain premature NK cells. Specific culture conditions are required to induce differentiation of the HSCs to pNKs (e.g., paragraph bridging pages 23-24; page 25).

No working examples of the claimed method are provided. No working examples are provided that demonstrate the ability of exogenously added ferritin H chain gene to induce pNK cell differentiation to form mNK cells in the presence of IL-15 protein. Differentiation of pNK cells to mNK cells in the presence of IL-15 protein and OP9 stromal cells is shown. However, differentiation of pNK cells to mNK cells absence of OP9 stromal cells is not shown for ferritin H chain gene.

Predictability and State of the art: The state of the art with regard to involvement of ferritin H gene in controlling the differentiation of pNK cells to mNK cells was underdeveloped at the time the invention was made. The prior art teaches that ferritin is a ubiquitous and highly conserved iron-binding protein composed of two subunits termed H and L (Torti et al. The Journal of Biological Chemistry, Vol. 263, No. 25, pages 12638-12644, 1988, cited in a prior

action; e.g., page 12638, right column, 3rd full paragraph). Torti et al teach that ferritin functions in the storage and delivery of iron for intracellular use, and it functions in detoxification of elemental iron, which is toxic in a non-complexed form (e.g., page 12638, right column, 3rd full paragraph). Thus the prior art does not provide clear support for a role for ferritin H chain gene (BC012314) in natural killer cell differentiation, and the specification does not provide evidence that increased expression of ferritin H chain gene (BC012314) by delivering the nucleic acid sequence of SEQ ID NO: 49 to incubated HSCs or pNK cells in combination with IL-15 will be sufficient to induce differentiation to mNK cells. Accordingly, the effects of exogenous ferritin H chain gene expression on natural killer cell differentiation would have been unpredictable.

Furthermore, it would have been unpredictable to obtain pNK cells from HSCs when the only step performed is incubating the HSCs. The specification teaches that HSCs must be differentiated in vitro under a specific set of culture conditions (e.g., paragraph bridging pages 23-24; page 25). Thus, mere incubation of HSCs would not be expected to produce pNK cells.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. One would be required to perform a large amount of trial and error experimentation to use the ferritin H chain gene and IL-15 protein to induce the differentiation of incubated HSCs or pNK cells to mNK cells. The prior art does not teach a role for ferritin H chain in the differentiation of NK cells, the specification does not provide evidence that ferritin H chain gene in combination with IL-15 protein is sufficient to induce NK cell differentiation, and the specification teaches detectable expression of ferritin H chain in HSCs, pNK cells, and mNK cells by RT-PCR. Thus, ferritin H chain

expression would already be present in the differentiating cells. It would require a large quantity of trial and error experimentation by the skilled artisan to carry out the claimed invention.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 29 and 38 are not considered to be enabled by the instant specification.

Response to Amendment – Declaration of Dr. Inpyo Choi

The declaration under 37 CFR 1.132 filed 10/27/2010 is insufficient to overcome the rejection of claims 29 and 38 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph, as set forth above. The evidence presented is not commensurate in scope with the claims.

The claimed invention requires the administration of a ferritin H chain gene of SEQ ID NO: 49 and IL-15 protein. The claims are not drawn to the administration of ferritin H chain protein and IL-15 protein.

At paragraph 8, the declaration states that to confirm whether pNK-specific expression of Ferritin H was required for the differentiation into mNK, hematopoietic stem cells (HSCs) were cultured for 6 days, and then treated with IL-5 protein and ferritin H protein in the absence of OP9 stromal cells, followed by measuring the percentage of NK cells. At paragraph 9, the declaration discusses the specific culture conditions required to differentiate HSCs to pNK cells. At paragraph 10, HSCs were treated with IL-15 protein only or OP9 stromal cells and IL-15 protein. At paragraph 11, it is stated that the percentage of NK cells was increased more when

the HSC, which were differentiated to pNK cells, were treated with IL-15 and ferritin H chain protein together, as opposed to when the cells were treated with IL-15 protein alone. The results of the experiment are shown in Exhibit B. At paragraph 12, it is disclosed that 14% NK1.1+ cells were obtained with IL-15 protein alone versus 23% when treated with IL-15 protein and 1 μg/ml of Ferritin H chain protein together. At paragraph 13, it is disclosed that 39% NK1.1+ NKG2A/C/E+ cells were obtained with IL-15 protein alone versus 43% each when treated with IL-15 protein and 1 μg/ml of Ferritin H chain protein together. At paragraph 14, the declaration concludes that ferritin H plays an important role in the differentiation from pNK cells into mNK cells and the search of genes regulating NK cell differentiation was correctly done in the present application.

The evidence is not commensurate in scope with the claimed invention. The declaration does not demonstrate that the Ferritin H chain gene of SEQ ID NO: 49 in combination with IL-15 protein is sufficient to differentiate pNK cells into mNK cells.

The evidence presented is not sufficient to overcome the prima facie case of non-enablement.

Response to Arguments - 35 USC § 112

With respect to the rejection of claims 29 and 38 under 35 U.S.C. 112, first paragraph (new matter), Applicant's arguments filed 10/27/2010 have been fully considered but they are not persuasive.

The reply filed 10/27/2010 asserts that support for the amendments can be found in the Examples section of US Patent Application Publication No. 2007/0042344.

The Examples section of the originally filed specification for the present application does not disclose the administration of ferritin H chain gene and IL-15 protein, at the same time, to premature NK cells. The Examples disclose the administration of IL-15 protein without ferritin H chain gene. The originally filed specification discloses the use of one or more genes to regulate the differentiation of natural killer cells (e.g., paragraph bridging pages 6-8). The originally filed specification discloses the use of one or more genes to regulate the differentiation of premature natural killer cells into mature natural killer cells, including the administration of the ferritin H chain gene (BC012315) (e.g., paragraph bridging pages 8-9). The originally filed specification does not disclose the administration of ferritin H chain gene and IL-15 protein to premature NK cells.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the passages that Applicant has provided do not provide support.

For these reasons and the reasons made of record above, the rejection is maintained.

With respect to the rejection of claims 29 and 38 under 35 U.S.C. 112, first paragraph (enablement), Applicant's arguments filed 10/27/2010 have been fully considered but they are not persuasive.

The response asserts that the Examiner criticizes the language "a stem cell to a natural killer cell." The response traverses the rejection but does not provide specific arguments. It is states that it is believed that the presently claimed invention directed to treating premature NK cells is fully enabled by the specification.

These arguments are not found persuasive. The first step of claim 29 is drawn only to the incubation of HSCs to produce premature NK cells. The specification teaches that more than mere incubation is required to produce premature NK cells. HSCs must be differentiated to pNK cells using specific culturing conditions (e.g., paragraph bridging pages 23-24; page 25). Furthermore, a review of the declaration indicates that the experiments are only directed to the differentiation of pNK to mNK in the presence of ferritin H chain protein and IL-15 protein. For the reasons discussed above with regard to the Declaration of Dr. Choi, these results are not commensurate in scope with the claims. No explanation or rationale is provided as to how the intracellular expression of ferritin H chain protein from the sequence of SEQ ID NO: 49 will have the same effect as exogenously added ferritin H chain protein in the culture medium as described by Dr. Choi in the declaration.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636